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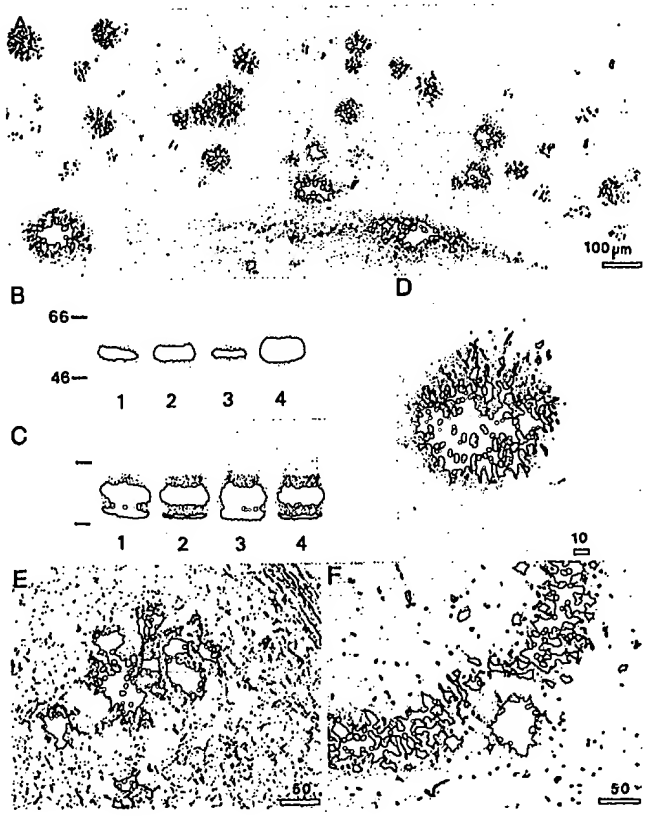
(54) Title: TRANSGENIC ANIMAL MODEL FOR ALZHEIMER DISEASE

(57) Abstract

The invention provides transgenic non-human animals which exhibit both APP and tau-linked features, e.g. histological features, of AD pathology, and preferably also behavioural changes characteristic of AD. Suitably the transgenic non-human animals express a human APP comprising the Swedish mutation or the Swedish mutation in combination with one or more additional mutations, in particular the London mutation. It appears that the level at which the transgene is expressed in the transgenic animal, e.g. the level of transgene mRNA, is an important factor for obtaining AD pathology in the animal. Transgenic mice expressing said mutated human APP under control of Thy-1 promoter element have been found to develop a pathological phenotype which goes beyond that previously described by Games et al. [Nature 373, 523-527, (1995)], by combining APP and tau-linked features of the AD pathology. Moreover, the mice have been found to present behavioural changes characteristic of AD, which has also never been reported before with transgenic animals.



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TRANSGENIC ANIMAL MODEL FOR ALZHEIMER DISEASE

The present invention relates to an animal model useful for testing potential therapeutic agents for the treatment of neurodegenerative disorders, in particular Alzheimer's disease (AD).

More particularly the invention relates to an animal model involving transgenic manipulation of amyloid precursor protein (APP).

The lack of an experimental animal model for AD that reflects the pathological mechanisms is a major obstacle for both basic research and drug development. As one approach to such models, reproduction of characteristic lesions such as senile plaques, neurofibrillary pathology, and cell loss in certain areas of hippocampus and cortex can be attempted. However, it is presently unclear whether these lesions are cause or consequence of the disease process. An alternative approach for model generation is to use factors known to lead to the disease. Recently, genetic studies revealed mutations in APP, which cosegregate with early onset of familial AD in the fifth or sixth decade of life and follow an autosomal dominant inheritance pattern. Three distinct missense mutations affect codon 717 of APP (altering V717→I {hereinafter referred to as the London mutation}, V717→G and V717→F in the polypeptide), while codons 670/671 (altering K670→N and M671→L in the polypeptide, hereinafter referred to as the Swedish mutation) are altered in the APP gene of a Swedish AD pedigree (numbers according to APP770). These mutations flank the part of APP that gives rise to βA4, the principal component of the filaments deposited in plaques in the brains of AD patients. In vitro studies have indicated that the Swedish mutation leads to increased formation of a soluble form of βA4, while the APP717 mutations gives rise to a higher proportion of a longer βA4 variant which facilitates filament formation. Together with the finding that filamentous βA4 is toxic in vitro, this suggests that the APP mutations may lead to AD via a mechanism involving βA4, but other mechanisms cannot be excluded.

More recently, transgenic mice have been generated, expressing APP with mutations in codons 717 and 670/671, using several neuron-specific promotors to drive expression

of human APP cDNAs. Although protein levels reaching or exceeding the amount of endogenous APP have been obtained, the full pattern of histological alterations characteristic of AD have not been seen in the transgenic mice.

It has now surprisingly been found that by appropriate selection of APP expression construct, high levels of transgene mRNA are obtained, which exceed the endogenous APP message by up to 10 fold, and result in correspondingly elevated protein levels. Moreover, on histological analysis, significant deposits of human βA4 peptide are observed. Additionally and even more importantly, hyperphosphorylation of the microtubule-associated protein tau is achieved, which is a pathological phenotype associated to AD. Furthermore, the deposits accumulate cholinesterase staining associated with a local distorsion of cholinergic fibers typically observed in AD. Both features have not been reported previously with analogous transgenic animals. The pathology is accompanied with selective neuron loss in distinct areas of the brain.

Accordingly in a first aspect the invention provides a recombinant DNA construct comprising a polynucleotide encoding a human APP polypeptide comprising the Swedish mutation, functionally linked to a Thy-1 promoter element, provided that the Thy-1 promoter element is a rodent, e.g. mouse, Thy-1 promoter element when the Swedish mutation is the only mutation present in the APP polypeptide.

Transgenic mice expressing said mutated human APP under control of said promotor have been found to develop a pathological phenotype which goes beyond that previously described by Games et al. [Nature 373, 523-527 (1995)], by combining APP and tau linked features of the AD pathology. Moreover, the mice have been found to present behavioural changes characteristic of AD, which has also never been reported before with transgenic animals.

It will be appreciated that such mice, by closely reflecting the AD pathology, as well as their transgenic cells, are particularly useful models of the disease.

Accordingly in a further aspect the invention provides transgenic non-human animals which exhibit both APP and tau-linked features, e.g. histological features, of AD pathology, and preferably also behavioural changes characteristic of AD.

Suitably the transgenic non-human animals express a human APP comprising the Swedish mutation or the Swedish mutation in combination with one or more additional mutations, in particular the London mutation. Suitably also the transgenic animal

exhibits the features of AD pathology before 12 months of age preferably by about 6 months of age. Conveniently the transgenic animal is a rodent e.g. a mouse or a rat, preferably a mouse. This aspect of the invention includes transgenic cells derived from the transgenic non-human animal.

Without prejudice to the generality of the present invention, it appears that the level at which the transgene is expressed in the transgenic animal e.g. the level of transgene mRNA, is an important factor for obtaining AD pathology in the animal.

Thus in a further aspect the present invention provides a transgenic non-human animal cell, wherein DNA coding for a human APP having only one mutation is expressed at such a level that the amount of transgene mRNA exceeds the endogenous APP message by about 5 times, e.g. from 3 to 6 times, or more, e.g. from about 5 to about 10 times, as well as a transgenic non-human animal, e.g. a mouse or a rat, preferably a mouse, in the cells of which DNA coding for a human APP having only one mutation is expressed at such a level that the amount of transgene mRNA exceeds the endogenous message by about 5 times or more.

The only one mutation present in the APP polypeptide may comprise any APP mutation, including the Swedish mutation or the London mutation or other mutations at amino acid 717. Preferably the only one mutation is the Swedish mutation.

It furthermore appears that the number of genetic lesions influencing the production of βA4 introduced in a transgenic animal is another important factor for obtaining AD pathology in the animal.

The invention also provides a transgenic non-human animal cell, wherein DNA coding for a human APP having 2 mutations is expressed at such a level that the amount of transgene mRNA exceeds the endogenous APP message by about 2 times, e.g. from 1.5 to 3 times, as well as a transgenic non-human animal, e.g. a mouse or a rat, preferably a mouse, in the cells of which DNA coding for a human APP is expressed at such a level that the amount of transgene mRNA exceeds the endogenous message by about 2 times.

Further the invention provides a transgenic non-human animal cell, wherein DNA coding for a human APP having 3 or more mutations is expressed at such a level that the amount of transgene mRNA exceeds the endogenous APP message by less than 2 times, e.g. from about 1 to 2 times, as well as a transgenic non-human animal, e.g. a

mouse or a rat, preferably a mouse, in the cells of which DNA coding for a human APP is expressed at such a level that the amount of transgene mRNA exceeds the endogenous message by less than 2 times.

The 2 mutations or 3 or more mutations may comprise any combination of 2 or 3 or more APP mutations. Preferably, however, such multiple mutations comprise a combination of the Swedish and London mutations.

The DNA coding for human APP may comprise cDNA and/or genomic DNA, and is conveniently cDNA.

More particularly the present invention provides a transgenic non-human animal cell, wherein DNA encoding a human APP polypeptide comprising the Swedish mutation is expressed under the transcriptional control of a Thy-1 promotor element, as well as a transgenic non-human animal, e.g. a mouse or a rat, preferably a mouse, in the cells of which DNA encoding a human APP polypeptide comprising the Swedish mutation is expressed under the transcriptional control of a Thy-1 promotor element, provided that when the Swedish mutation is the only mutation present in the APP polypeptide the Thy-1 promoter element is a rodent, e.g. mouse, Thy-1 promoter element.

Transgenic animals according to the invention include animals into which the construct has been introduced directly as well as progeny of such animals which retain the ability to express the construct.

Cells manipulated according to the invention may be prepared by any known transfection technique. The DNA sequence may be introduced by direct genetic manipulation or into an earlier generation of the cell. Thus, the cells may be obtained from transgenic animals and cultured *in vitro*.

Also the transgenic animals may be generated according to well established methods, such as manipulation of embryos, e.g. by gene transfer into embryonic stem cells, retroviral infection of early embryos or pronuclear microinjection.

The pronuclear microinjection technique is preferred. Transcription units obtained from a recombinant DNA construct of the invention are injected into pronuclei of animal embryos and the obtained founder transgenics are bred.

The results obtained in the offspring can be analysed using various techniques well known in the art. Thus, for example, transgene APP mRNA expression is analysed by RNA blotting, the expression pattern of the transgene in the brain is determined by *in situ* hybridization, detection of APP in the brain is effected using immunoblotting techniques (western blot analysis) and the effects of the expression are studied by histology and immunohistology.

Models based on cells and animals of the invention may be used for example to identify and assess the efficacy of potential therapeutic agents in neurodegenerative diseases, particularly in diseases where βA4 peptide is deposited and/or the microtubule-associated protein tau is hyperphosphorylated, more particularly in AD. In particular such models may be used in screening or characterization assays for detecting agents likely to prevent βA4 deposit and/or hyperphosphorylation of tau.

Accordingly in a further aspect the invention comprises a method for testing a potential therapeutic agent for a specified condition, in particular a neurodegenerative disease, preferably AD, wherein a cell of the invention is used as target cell. More particularly it comprises such a method, wherein the agent is administered to a transgenic non-human animal of the invention. Moreover the invention comprises a screening or characterization assay consisting in or including such a method, as well as a screening assay kit comprising cells of the invention.

Methods for screening potential therapeutic agents using cell lines or animals are well known in the art. The cells and animals of the present invention may be used in analogous manner.

The recombinant cells may for example be incubated with the potential therapeutic agent and with antibodies recognizing βA4 amyloid in typical senile and diffuse plaques and/or with tau antibodies staining neurofibrillary tangles in the Alzheimer brain. In methods where the transgenic animals themselves are used, the effects of the potential therapeutic agent may be determined by carrying out various investigations on the animals after sacrifice. Also after administration of the potential therapeutic agent, the transgenic animal may undergo behavioural testing in order to monitor cognitive function.

The techniques of detection of βA4 and protein tau, including Western blot analysis, and the antibodies used therefor, are also well documented.

Compounds for use in the treatment of neurodegenerative diseases, which have been identified using an assay or assay kit as defined above, are also part of the present invention.

The following example illustrates the invention:

Expression construct

Human APP751 cDNA carrying the Swedish double mutation is modified at the 5' end to reconstitute an optimal translation initiation sequence (GCC GCC ATG G).

This cDNA starting at above sequence and extending to nucleotide 3026 (Hind III site) is inserted into the Xho I cloning site of a pUC18-based vector containing an 8.1 kb EcoRI fragment comprising the mouse Thy-1.2 gene [Vidal et al. (1990) EMBO J. 9, 833-840]. The vector is modified such that a 1.5kb BanI-XhoI fragment carrying exon 3 and flanking intervening sequences is replaced by a linker sequence encoding the unique Xho I recognition site [Moechars et al. (1996) EMBO J. **15**, 1265-1274]. Transcription units are released by NotI/PvuI digestion.
Expression construct APP 14 described in K. Andrä et al., Neurobiology of Aging, Vol. 17, No. 2, 183-190 (1996) is modified by replacing a 600 bp Bgl II/Spe I fragment with a corresponding fragment of a human APP_{751} cDNA carrying the London mutation V 717 → I. Transcription units are released by Not I digestion.

Generation of transgenic mice

Isolated transcription units are injected into the pronuclei of B6D2F1 x B6D2F1 embryos to generate transgenic founder animals.

Northern blot analysis, in situ hybridization, western blot analysis, histology and immunohistology

are performed according to the methods described in K. Andrä et al., Neurobiology of Aging, Vol. 17, No. 2, 183-190 (1996).

Results

Offspring of the founder animals express human APP mRNA in high amounts throughout all brain structures as demonstrated by *in situ* hybridization. Determined amounts of transgene derived protein exceed those of endogenous APP 5 to 10 fold. At 6 months of age, these mice show extracellular deposits of human βA4 peptide in cerebral cortex and the hippocampal formation. These deposits are positive in methenamine silver impregnation, thioflavin S staining and in Congo Red birefringence. They are surrounded by reactive astrocytes and dystrophic neurites. In addition, plaques are immunoreactive with antisera specific to hyperphosphorylated microtubule associated protein tau as found in brains of AD patients, which has not been reported previously for analogous transgenic animals. Hence, the described deposits in the brains of these mice closely resemble senile plaques found in AD patients. When stained for acetylcholinesterase, a strong labelling of plaques and a local distorsion of the cholinergic fibre network is observed. Plaques contain acetylcholinesterase activity in structures resembling swollen, dystrophic neurites. This degeneration of cholinergic neurites is another well-known feature associated with AD. Furthermore, a local degeneration of neurons in the plaque vicinity is observed in areas typically affected in AD such as hippocampal CA1. Here, the neuron loss is negatively correlated to the plaque burden and can reach up to 20%.

Tau hyperphosphorylation, cholinesterase staining and neuron loss in APP transgenic mice according to the invention are illustrated in Figure 1. Staining of plaques with tau antibody AT8 recognizing phosphorylated Ser202 and Thr205 of tau is shown on a sagital free floating section of a transgenic mouse brain in A and in higher magnification in D. Western blots of brain extracts from transgenic mice, 6 months (2) and 15 months (4) of age and littermate controls (1,3) are shown in B and C. Blots were stained with antibodies AT8 (B) and N-tau7 (C) recognizing tau in a phosphorylation dependent and independent manner, respectively. Numbers indicate molecular weights of marker proteins in kDa. E shows staining for acetylcholine esterase in transgenic mice. A local distorsion of cholinergic fibers in the plaque vicinity can be noted. The loss of pyramidal neurons in the vicinity of Aß deposits in area CA3 is shown in F by toluidine blue staining.

Behavioural testing

Transgenic mice obtained as described above show significant non-cognitive behavioural changes corresponding to changes observed with patients suffering from AD, as reported by Mega et al. (1996) Neurology **46**, 130-135.

For example in the Half-Enclosed Platform test according to a modification of Käsermann (1986) Psychopharmacol. **89**, 31-37, compared to non-transgenic littermates, the animals avoided the open half and an increase of exploratory-behavioural moves and postures such as locomotion and head raising, indicative of agitation, disinhibition and irritability as reported for AD patients was observed.

Cognitive testing

Furthermore the mice show significant cognitive impairment.

For example in the water maze according to Morris et al. (1982) Nature **297**, 681-683, compared to non-transgenic littermates, the animals made significantly less crossings of the annulus representing the platform's previous position (2.5 ± 0.5 vs. 4.4 ± 0.7; $p < 0.05$, 2-tail Mann-Whitney U-test) and spent a significantly lower percentage of time in the quadrant containing the annulus (20.8 ± 3.8 vs. 33.1 ± 3.2; $p < 0.05$, 2-tail Mann-Whitney U-test).

CLAIMS

1. A recombinant DNA construct comprising a polynucleotide encoding a human APP polypeptide comprising the Swedish mutation, functionally linked to a Thy-1 promoter element, provided that the Thy-1 promoter element is a rodent, e.g. mouse, Thy-1 promoter element when the Swedish mutation is the only mutation present in the APP polypeptide.

2. A recombinant DNA construct according to claim 1, in which the APP polypeptide additionally comprises the London mutation.

3. A recombinant DNA construct according to claim 1 or 2, in which the Thy-1 promoter element is a human Thy-1 promoter element.

4. A transgenic non-human animal which exhibits both APP and tau-linked features of AD pathology, and preferably also behavioural changes of AD, and transgenic cells thereof.

5. A transgenic non-human animal cell, wherein DNA encoding a mutant human APP comprising only one mutation is expressed at such a level that the amount of transgene mRNA exceeds the endogenous message by about 5 times or more.

6. A transgenic non-human animal cell according to claim 5 in which the only one mutation is the Swedish mutation.

7. A transgenic non-human animal cell, wherein DNA encoding a mutant human APP comprising two mutations is expressed at such a level that the amount of transgene mRNA exceeds the endogenous message by about 2 times

8. A transgenic non-human animal cell according to claim 7 in which the two mutations are the Swedish mutation and the London mutation.

9. A transgenic non-human animal cell, wherein DNA encoding a mutant human APP comprising the three or more mutations is expressed at such a level that the amount of transgene mRNA exceeds the endogenous message by 2 times or less.

10. A transgenic non-human animal cell, wherein DNA encoding a human APP polypeptide comprising the Swedish mutation is expressed under the transcriptional control of a Thy-1 promoter element, provided that when Swedish mutation is the only mutation present in the APP polypeptides the Thy-1 promoter element is a rodent, e.g. mouse, Thy-1 promoter element.

11. A transgenic non-human animal cell according to claim 10, in which the human APP polypeptide additionally comprises the London mutation.

12. A transgenic non-human animal cell according to claim 11, wherein the Thy-1 promoter element is a human Thy-1 promoter element.

13. A transgenic non-human animal, in the cells of which DNA encoding a human APP having only one mutation is expressed at such a level that the amount of transgene mRNA exceeds the endogenous message by about 5 times or more.

14. A transgenic non-human animal according to claim 13, in which the only one mutation is the Swedish mutation.

15. A transgenic non-human animal, in the cells of which DNA encoding a human APP having two mutations is expressed at such a level that the amount of transgene mRNA exceeds the endogenous message by about 2 times.

16. A transgenic non-human animal according to claim 15, in which the two mutations are the Swedish mutation and the London mutation.

17. A transgenic non-human animal, in the cells of which DNA encoding a human APP polypeptide comprising the Swedish mutation is expressed under the transcriptional control of a Thy-1 promoter element, provided that when the Swedish mutation is the only mutation present in the APP polypeptide the Thy-1 promoter element is a rodent, e.g. mouse, Thy-1 promoter element.

18. A transgenic non-human animal according to claim 17 in which the APP polypeptide additionally comprises the London mutation.

19. A transgenic non-human animal according to claim13 to 18, which is a mouse.

20. A method of producing a transgenic non-human animal, wherein said animal is generated by incorporating a recombinant DNA construct according to claim 1 into its genome.

21. A method of producing transgenic non-human animals capable of developing a neurodegenerative disease pathology, comprising injection of transcription units obtained from a recombinant DNA construct according to claim 1 into pronuclei of non-human animal embryos and breeding the so obtained founder animals.

22. A method for testing a potential therapeutic agent for a specified condition, wherein a transgenic animal according to any one of claims 13 to 19 is used or a cell according to claim 5 to 12 is used as target cell.

23. A method according to claim 22, wherein the agent is administered to a transgenic non-human animal produced according to the method of claim 20 or 21.

24. A method according to claim 22, wherein the condition is a neurodegenerative disease.

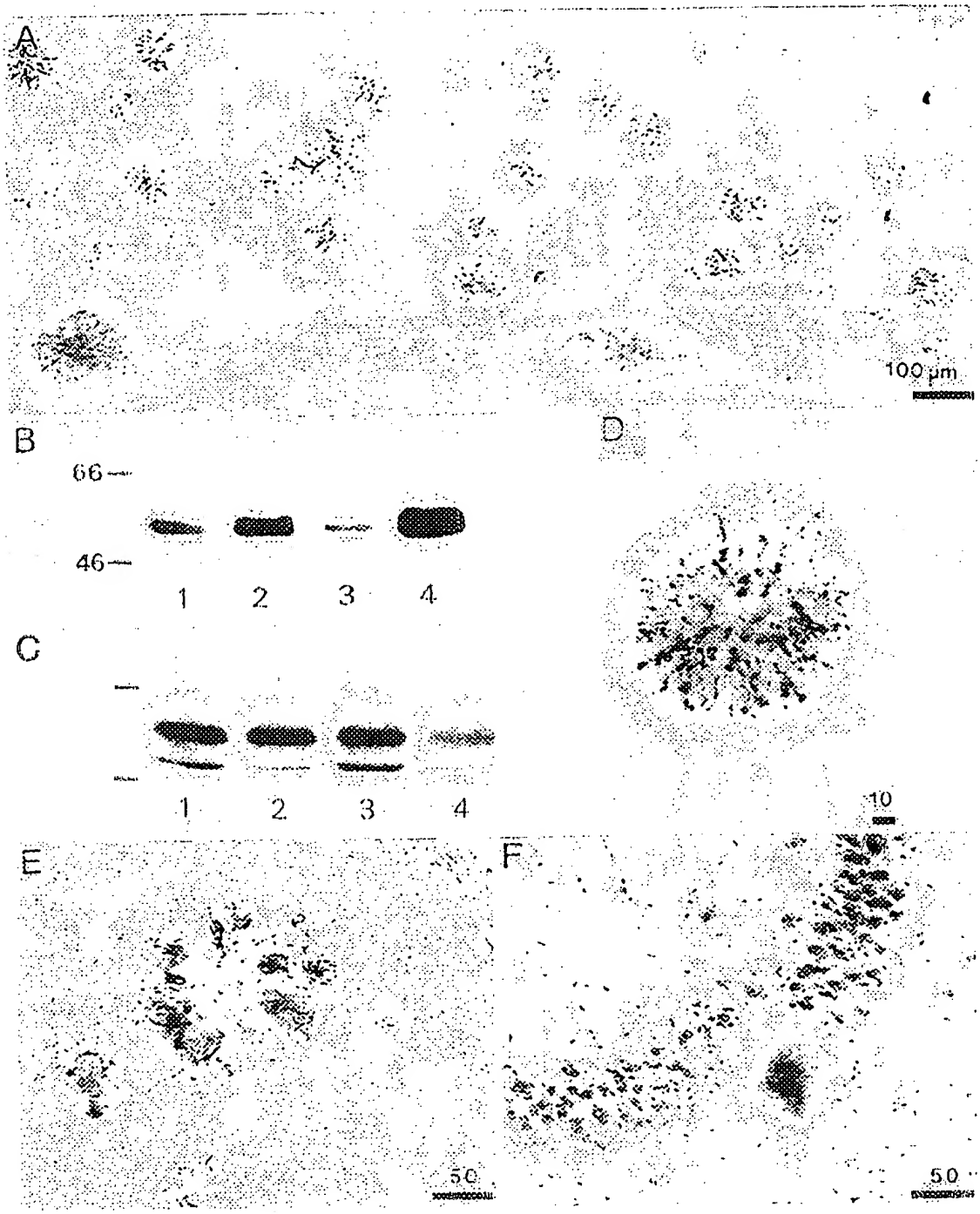
25. A method according to claim 22, wherein the condition is Alzheimer's disease.

26. A screening or characterization assay consisting in or including a method according to any one of claims 23 to 25.

27. A screening assay kit comprising cells according to any one of claims 5 to 12.

28. A compound for use in the treatment of a neurodegenerative disease, which has been identified using an assay or assay kit according to claim 26 or 27.

fig.1



INTERNATIONAL SEARCH REPORT

Inte. ,onal Application No
PCT/EP 97/03991

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/00 A01K67/027 C07K14/47 C12N15/12 A61K49/00

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A01K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	GAMES D ET AL: "ALZHEIMER-TYPE NEUROPATHOLOGY IN TRANSGENIC MICE OVEREXPRESSING V717F BETA-AMYLOID PRECURSOR PROTEIN" NATURE, vol. 373, no. 6514, 9 February 1995, pages 523-527, XP000602050 see the whole document ---	4,5,13, 22-26,28
X	ANDRA, K. ET AL.: "Expression of APP in transgenic mice : a comparison of neuron-specific promoters" NEUROBIOLOGY OF AGING, vol. 17, no. 2, 23 May 1996, pages 183-190, XP002049072 see the whole document ---	5

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[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
3 December 1997	23/12/1997

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 94 12627 A (CEPHALON INC) see claims 1-4,9-111,13-28	4
A	WO 93 14200 A (TSI CORP) see the whole document	1
P,X	SOMMER, B. ET AL.: "Animal models for Alzheimer's disease based on genetic and pathology" SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 22, no. 1-3, 16 - 21 November 1996, page 25 XP002049073 see the whole document	1

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. .onal Application No
PCT/EP 97/03991

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